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## CLINICAL RESEARCH

# Cryoballoon for pulmonary vein isolation: Is it better tolerated than radiofrequency? Retrospective study comparing the use of analgesia and sedation in both ablation techniques

L'isolation des veines pulmonaires par la cryoablation au ballon : est-ce mieux tolérée que la radiofréquence? Étude rétrospective comparant l'utilisation de médicaments antalgiques et anesthésiques au cours des deux techniques

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### Summary

**Background.** — Treatment of atrial fibrillation (AF) by radiofrequency or cryoballoon ablation requires good sedation and effective analgesia to be carried out safely and successfully.

**Aim.** — To compare analgesic and sedative drug usage during ablation procedures for paroxysmal AF.

**Methods.** — The records of 60 patients hospitalized for ablation of paroxysmal AF were studied. Patients were divided into two groups, according to the technique used: radiofrequency ablation (group A) and cryoballoon ablation (group B). Anaesthetic and sedative medication usage was compared between groups.

**Results.** — Patients' mean age was  $56.2 \pm 1$  years in the radiofrequency group and  $57.0 \pm 0.74$  years in the cryoballoon group; mean duration of AF was  $6.91 \pm 2.36$  and  $6.77 \pm 2.51$  years, respectively. Twenty patients from group A and 18 from group B had transesophageal echocardiography. With regard to sedative use,  $3.01 \pm 1.3$  mg/m<sup>2</sup> of midazolam was used in group A versus  $3.5 \pm 1.26$  mg/m<sup>2</sup> in group B ( $p=0.14$ ). Propofol was seldom used. For analgesia,

**Abbreviations:** AF, Atrial fibrillation; PV, Pulmonary vein; RF, Radiofrequency; TEE, Transesophageal echocardiography.

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**MOTS CLÉS**

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 Tolérance

$0.31 \pm 0.26 \text{ g/m}^2$  of paracetamol was used in group A versus  $0.73 \pm 1.86 \text{ g/m}^2$  in group B ( $p=0.23$ ). Mean morphine dose was higher in group A versus group B ( $3 \pm 1.5$  vs  $2.09 \pm 1.02 \text{ mg/m}^2$ , respectively;  $p=0.01$ ).

**Conclusion.** — In this study, patients who underwent cryoballoon ablation required a lower dose of morphine compared with those who underwent radiofrequency ablation. Catheter cryoballoon ablation appears better tolerated than radiofrequency ablation for the treatment of paroxysmal AF.

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**Résumé**

**Justification.** — L'ablation par radiofréquence ou par cryo-énergie de la fibrillation auriculaire (FA) nécessite une bonne sédation et une analgésie efficace.

**Objectif.** — Comparer les antalgiques et sédatifs durant les procédures d'ablation de FA paroxystique.

**Méthodes.** — Une étude rétrospective a été réalisée sur 60 patients hospitalisés pour ablation de FA paroxystique, divisés en deux groupes ; groupe A : radiofréquence, groupe B : cryoablation. Nous avons comparé l'utilisation des anesthésiques et sédatifs.

**Résultats.** — L'âge moyen était de  $56,2 \pm 1$  ans pour le groupe A et  $57 \pm 2,51$  pour le groupe B. L'ancienneté de la FA était de  $6,91 \pm 2,36$  ans pour le groupe A et de  $6,77 \pm 2,51$  pour le groupe B. Vingt patients du groupe A et 18 du groupe B ont eu une échocardiographie transœsophagienne. Concernant les sédatifs, les doses utilisées ont été :  $3,01 \pm 1,3 \text{ mg/m}^2$  de midazolam pour le groupe A et  $3,5 \pm 1,26 \text{ mg/m}^2$  pour le groupe B ( $P=0,135$ ). Le propofol était peu utilisé. Concernant les analgésiques, les doses utilisées ont été :  $0,31 \pm 0,26 \text{ g/m}^2$  de paracétamol pour le groupe A, contre  $0,73 \pm 1,86 \text{ g/m}^2$  dans le groupe B ( $P=0,23$ ) ;  $3 \pm 1,5 \text{ mg/m}^2$  de morphine dans le groupe A contre  $2,09 \pm 1,02 \text{ mg/m}^2$  dans le groupe B avec une différence significative ( $p=0,01$ ).

**Conclusion.** — La cryoablation nécessite moins d'analgésiques que la radiofréquence d'après notre étude. L'anesthésie légère offre une meilleure tolérance et assure un état de conscience vigile qui permet de détecter les complications de façon plus précoce.

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**Background**

AF is the most frequent arrhythmia in clinical practice, affecting 5% of people aged 65 years and 10% of those aged over 80 years [1,2]. PV isolation by RF or cryoballoon ablation enables effective treatment of paroxysmal AF [3].

Currently, RF is the gold standard ablation strategy for paroxysmal AF [3]. However, this technique can be complicated by stenosis of the PVs, thromboembolism, pericardial effusion, complex left atrial flutters and atrio-oesophageal fistula. Cryoballoon ablation has emerged as a valuable alternative to RF ablation in the treatment of AF, with complications that seem to occur less frequently. There has been no description of atrio-oesophageal fistula with cryoballoon ablation, while thromboembolic accidents and PV stenosis are exceptional [4]. This technique creates smaller, more circumscribed and reversible lesions, better stability for energy delivery, and greater patient comfort with a lower risk of pain [5].

In our experience, we can avoid and treat rapidly any complications that might arise while carrying out these techniques with the patient under conscious sedation, while maintaining appropriate pain management. We therefore initiated the present study to assess the requirements for pain control with the two ablation techniques; our aim was to compare the doses of analgesic and sedative drugs used

during the treatment of paroxysmal AF by RF ablation and cryoballoon ablation.

**Methods****Study population**

We studied the case files of 60 successive patients who had ablations after we considered that our proficiency in performing both techniques was optimal. Thirty patients had RF ablation for paroxysmal AF while 30 had catheter cryoballoon ablation for the same indication. Paroxysmal AF is defined as recurrent episodes of AF that self-terminate in less than 7 days. Patients who required a hybrid technique with additional RF at the end of a catheter cryoballoon ablation procedure were excluded.

Our retrospective study included the following variables: epidemiological data (age, sex, prior history); clinical data (weight, height, body surface area, duration of AF); ancillary data (whether TEE was used or not); and therapeutic data (ablation procedure [type of procedure, need for external cardioversion, results, complications], medication dosage [the medications used are expressed in  $\text{mg/m}^2$ ]).

Two groups were identified: group A (patients who had RF ablation) and group B (patients who had catheter cryoballoon ablation).

## Anaesthesia and analgesia

Conscious sedation was administered by a nurse at the direction of the physician. Initially, the patient received: sedatives (midazolam [Hypnovel®], 2–5 mg if TEE; propofol [Diprivan®], 20 mg if TEE difficult); analgesics (paracetamol [Perfalgan®], 1 g at the start of the procedure; morphine, 3 mg). These doses were titrated by the physician to achieve an adequate comfort level throughout the procedure. The use of morphine is not systematic and depends on the response to pain expressed by the patient through motion or verbal communication. Electrocardiographic tracing and continuous monitoring of heart rate, and respiratory and oxygen saturation were performed. Blood pressure was monitored non-invasively every 5 minutes. The doses of anaesthetic products were referenced to body surface area using the Boyd calculation formula (used most frequently in clinical research) [6]: body area (m<sup>2</sup>) = 0.0003207 × (weight)<sup>0.7285-0.0188 × log (weight)</sup> × (height)<sup>0.3</sup>; weight is in g (limit, 15–200 kg), height is in cm (limit, 99–250 cm) and the log is decimal.

Anaesthetic and sedative medication dosages were compared between the two groups.

## Radiofrequency procedure

For RF ablation, we used the same procedure as that described by Haïssaguerre and coworkers [7]. After placing diagnostic catheters into the coronary sinus, the interatrial septum was punctured as described before, and venography of all four PVs was performed by introducing contrast material through the transseptal sheath or through a 6-French multipurpose catheter into the proximal PVs. Next, a circumferential mapping catheter (Lasso, Biosense Webster Inc., Diamond Bar, CA, USA) was introduced into the proximal PVs. An irrigated tip ablation catheter (ThermoCool, Biosense Webster Inc., Diamond Bar, CA, USA) delivering RF energy was introduced into the same hole. RF was applied in a power-controlled mode with a power limit of 30 W and a maximum temperature of 48 °C. Ablation was performed at the atriovenous junction proximal to the circumferential mapping catheter at sites showing the earliest PV potentials, performing a segmental ablation of the PV ostia.

As in the cryoballoon group, acute isolation success was confirmed by the circumferential Lasso catheter in all patients. Also, 20 minutes after the last PV was ablated, ablation success was verified again in all PVs. Periprocedural and postprocedural anticoagulants were administered.

## Cryoballoon procedure

All patients were treated with a double-lumen cryoballoon (Arctic Front, CryoCath Technologies, Montreal, Quebec, Canada), either 23 mm or 28 mm in size, as appropriate for the diameter of the PVs. Both femoral veins were used for venous access. A multipolar catheter (Woven, Bard Electrophysiology Inc., Lowell, MA, USA) was placed in the coronary sinus via the left femoral vein. Via the right femoral vein, we used a single standard transseptal approach with a Brockenbrough needle (BRK Needle, St Jude Medical, St. Paul, MN, USA) guided by fluoroscopy and TEE, as required. We introduced an 8-French SL1 sheath (FAST-CATH, St. Jude Medical,

St. Paul, MN, USA) into the left atrium, then performed angiography of the PV with the catheter. We advanced and positioned a 10-pole Lasso catheter (Lasso 2515, Biosense-Webster Inc., Diamond Bar, CA, USA) in the antrum of each vein to demonstrate the presence of electrical activity in the veins. For the left PV, pacing in the distal coronary sinus was necessary to confirm PV potentials. After this confirmation, we proceeded with the ablation without continuous Lasso monitoring.

We removed the SL1 sheath and advanced a 12-French steerable sheath (FlexCath, CryoCath Technologies, Montreal, Quebec, Canada) “over the wire” (0.032 inch, 180 cm Super Stiff G.W., St Jude Medical, St. Paul, MN, USA) into the left atrium. The Arctic Front balloon catheter was introduced inside the 12-French sheath and positioned over a wire guide (Amplatz Extra Stiff Wire Guide, 0.032 inch, Cook Group Incorporated, Bloomington, IN, USA). We selected either a 23 mm or a 28 mm Arctic Front cryoballoon in accordance with PV diameters. The cryoballoon catheter was positioned in such a way as to occlude the ostium of each PV after inflation. Cryoablation was applied for 4 minutes at least twice for each vein and directed toward the major side branches with the use of the guide wire. We tried for at least one cryoablation application with full occlusion (grade 4) on each targeted vein. When the extent of occlusion was not optimal, we changed the position of the balloon or flexion of the sheath to achieve better occlusion. The ablation procedure was always started in the left superior PV, then proceeded to the left inferior PV, followed by the right inferior PV, and finally, the right superior PV.

Whenever we targeted the right PVs, we positioned the Lasso catheter in the superior caval vein for continuous phrenic nerve stimulation during cryoablation application. As the proximity of the phrenic nerve to the right-sided veins cannot be ascertained, this vigilance is essential in order to prevent phrenic nerve palsy. If phrenic nerve capture ceased, the ablation was stopped instantly due to the operator's continuous monitoring. After targeting all the PVs, we reintroduced the Lasso catheter into the veins to verify that complete electrical disconnection was achieved during sinus rhythm and pacing. The procedure was performed under full anticoagulation with heparin.

## Statistical analysis

Statistical analysis was done using the SPSS software program, version 10.0 (SPSS Inc., Chicago, IL, USA). The variables studied were expressed as means ± standard deviations.

Continuous data were compared between the two groups by the unpaired *t*-test and ordinal data were compared in both groups using the chi-square test. A value of *p* < 0.05 was considered to be statistically significant.

## Results

The demographic and anthropometric characteristics of both groups are summarized in Table 1.

For the population in group A, the mean duration of AF was 6.91 ± 2.36 years (range, 0.16–30 years) and the underlying diseases were four cases of hypothyroidism and one

**Table 1** Comparison of epidemiological and morphological data in the two groups.

Variable	Group A (Radiofrequency group) (n = 30)	Group B (Cryoablation group) (n = 30)	P value
Age (years)	56.2 ± 1 (range 78–32)	57 ± 2.51 (range 77–43)	0.94
Sex ratio (men/women)	2.5:1	4:1	0.55
Weight (kg)	74.16 ± 2.3 (104–47)	76.6 ± 2.1 (110–53)	0.84
Height (m)	1.71 ± 0.3 (1.8–1.5)	1.72 ± 0.5 (1.9–1.5)	0.99
Body surface area (m <sup>2</sup> )	1.88 ± 1.7 (2.3–1.48)	1.92 ± 1.2 (2.42–1.56)	0.98
Data (other than sex ratio) are mean ± standard deviation (range).			

**Table 2** Proportion and comparison of patients who had transesophageal echocardiography in the two groups.

	Group A(Radiofrequency group)(n = 30)	Group B(Cryoablation group)(n = 30)	P value
TEE+	20 (66.7)	18 (60.0)	0.74
TEE–	10 (33.3)	12 (40.0)	0.66
Data are number (%). TEE+: patients required transesophageal echocardiography; TEE–: patients did not require transesophageal echocardiography.			

case, respectively, of hyperthyroidism, tachycardia-induced cardiomyopathy, valvular heart disease and sick sinus syndrome. For the population in group B, the mean duration of AF was  $6.77 \pm 2.51$  years (range, 1–22 years) and the underlying associated diseases were four cases of hypothyroidism and one of tachycardia-induced cardiomyopathy.

TEE was carried out inside the catheter laboratory, in case of difficult transseptal puncture. Twenty patients (66.7%) in group A and 18 patients (60.0%) in group B required TEE ( $p = 0.74$ ; Table 2). Cardioversion was necessary for two patients in group B and one patient in group A at the end of the procedure.

In order to obtain good sedation and analgesia in our patients, we used sedatives such as midazolam and propofol and analgesics such as morphine and paracetamol. We compared the mean doses of these products in both groups (Table 3). Propofol was used in two patients in group A and four patients in group B.

In the immediate follow-up after the ablation, we noted four complications in group B (1.3%; one case of pericardial effusion, one case of self-limiting mediastinal effusion

and two cases of transient phrenic paralysis) and two complications in group A (0.6%; transient phrenic paralysis and pericardial effusion). The pericardial effusion was drained uneventfully.

## Discussion

This study concerned two techniques (RF and catheter cryoablation) in the treatment of paroxysmal AF.

Both groups of patients were similar in terms of demographic and anthropometric characteristics. Our study population had similar demographic and anthropometric characteristics to those of populations from other studies addressing similar pathology. In two recent studies on catheter cryoablation and RF ablation for paroxysmal AF, Klein et al. [8] and Reant et al. [9] found, respectively: mean age, 59 and 56 years; mean duration of AF, 6.5 and 9.2 years. These demographic and anthropometric data are similar to those found in our study.

**Table 3** Anaesthetic and analgesic drugs used during the ablation procedures in the two groups.

Drugs	Population	Number of patients	Mean	Standard deviation	P value
Midazolam (mg/m <sup>2</sup> )	Group A	30	3.01	1.35	0.135
	Group B	30	2.50	1.26	
Morphine (mg/m <sup>2</sup> )	Group A	30	3.0	1.53	0.010
	Group B	30	2.09	1.02	
Paracetamol (g/m <sup>2</sup> )	Group A	30	0.31	0.26	0.230
	Group B	30	0.73	1.86	

Group A is the radiofrequency group; group B is the cryoablation group.



Isolation of the PVs during AF ablation was carried out under light sedation and with intravenous analgesia. This enabled us to maintain the patient in a state of sufficient awareness to be able to warn us if there was any sign suggesting a complication. The complications we encountered were no different from the usual complications associated with ablation procedures for AF (pericardial effusion, mediastinal effusion and transient phrenic paralysis) [10]. The few complications recorded were spontaneously reversible. Of note, we did not recognize any embolic event in our 60 patients.

A comparison of the anaesthetic and analgesic medication used enabled us to estimate the pain associated with each of the two techniques. Additional procedures that necessitated an increase in anaesthetic or analgesic doses were carried out in similar proportions in both groups. Twenty patients (66.6%) in group A and 18 patients (60.0%) in group B had a TEE ( $p=0.74$ ). Cardioversion was required for one patient in group A and two patients in group B.

## Sedative and hypnotic drugs

Sedative and hypnotic drugs were used systematically at the beginning of the procedure, regardless of the technique used. Midazolam is a benzodiazepine with a short life (mean half-life, 3 hours [11]), which is used in most semi-invasive and invasive procedures in adults and children [12–14]; it provides lower anxiety and good sedation. For group A, a mean dose of  $3.01 \pm 1.3$  mg/m<sup>2</sup> of midazolam was used compared with  $3.5 \pm 1.26$  mg/m<sup>2</sup> for group B (non-significant difference;  $p=0.135$ ).

This lack of difference between the two groups is related to the fact that midazolam was administered systematically, irrespective of the procedure and the patient's anxiety. Propofol was seldom used in our patients (two patients in group A and four patients in group B); all these patients had TEE. This low usage of propofol is due to the fact that it is a product that has haemodynamic and respiratory side effects; it is very helpful if TEE is needed and its management often requires the presence of anaesthesia support [12].

## Intravenous analgesic drugs

Intravenous doses of paracetamol and morphine referenced to weight were administered systematically to patients at the beginning of the procedure. The doses of morphine were then increased depending on the pain felt by the patient. These symptoms were dominated by headaches and toothache in cryoballoon ablation, while back and shoulder pain occurred more frequently in RF applications.

In group A, a mean dose of  $0.31 \pm 0.26$  g/m<sup>2</sup> of paracetamol was used compared with  $0.73 \pm 1.86$  g/m<sup>2</sup> in group B (non-significant difference;  $p=0.23$ ); a mean dose of  $3 \pm 1.5$  mg/m<sup>2</sup> of morphine was used in group A compared with  $2.09 \pm 1.02$  mg/m<sup>2</sup> in group B (statistically significant difference;  $p=0.01$ ). It is apparent that a larger dose of morphine was used in patients who underwent RF compared with in those who underwent cryoballoon ablation. The increase in the dose of morphine in our series was related to the presence of often unbearable pain felt by the patient during ablation, generally during RF. These data confirm that

AF cryoballoon ablation, which uses a more gentle form of energy than RF, is better tolerated [15].

There were no complications relating to anaesthesia or analgesia in either group; these drugs are usually well tolerated and enable physicians to carry out procedures with greater safety levels [16].

## Study limitations

Although this was, to our knowledge, the first study concerning this matter, the number of patients enrolled was limited and it was not a randomized study. Even though there was a clearly statistically significant finding, we cannot entirely exclude it being due to chance. In addition, as there is no accurate means of measuring an individual patient's reaction to pain, this remains an entirely subjective assessment. It would be useful to compare the perception of pain in both groups on a visual analogue scale [17].

## Conclusion

The use of light anaesthetic and analgesic products decreases pain and anxiety in patients, while maintaining a state of consciousness, enabling them to alert the physician to pain during ablation procedures for paroxysmal AF. According to our study, catheter cryoballoon ablation required less analgesic than RF ablation. Catheter cryoballoon ablation would therefore seem to be better tolerated than RF ablation for the treatment of paroxysmal AF. Apart from this better tolerance, it is a technique that offers greater comfort for the practitioner, the patient and the nursing staff, as well as less risk of drug overdosing. The use of lower doses of anaesthetic products in catheter cryoballoon ablation makes this technique much simpler to use and involves less risk for the patient, theoretically. According to the available literature, our results are similar to those from other studies of RF in the treatment of paroxysmal AF.

A prospective study on the use of sedatives and analgesics, with collection of side effects and symptoms of patients during the ablation procedures for AF, would provide confirmation of current study findings.

## Conflict of interest statement

No conflict of interest.

## References

- [1] Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001;285:2370–5.
- [2] Zhou Z, Hu D. An epidemiological study on the prevalence of atrial fibrillation in the Chinese population of mainland China. *J Epidemiol* 2008;18:209–16.
- [3] Pappone C, Augello G, Sala S, et al. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study. *J Am Coll Cardiol* 2006;48:2340–7.

- [4] Lustgarten DL, Keane D, Ruskin J. Cryothermal ablation: mechanism of tissue injury and current experience in the treatment of tachyarrhythmias. *Prog Cardiovasc Dis* 1999;41:481–98.
- [5] Lowe MD, Meara M, Mason J, et al. Catheter cryoablation of supraventricular arrhythmias: a painless alternative to radiofrequency energy. *Pacing Clin Electrophysiol* 2003;26:500–3.
- [6] Boyd E. The growth of the surface area of the human body. Minneapolis: University of Minnesota Press; 1935. p. 1–145.
- [7] Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998;339:659–66.
- [8] Klein G, Oswald H, Gardiwal A, et al. Efficacy of pulmonary vein isolation by cryoballoon ablation in patients with paroxysmal atrial fibrillation. *Heart Rhythm* 2008;5:802–6.
- [9] Reant P, Lafitte S, Bougteb H, et al. Effect of catheter ablation for isolated paroxysmal atrial fibrillation on longitudinal and circumferential left ventricular systolic function. *Am J Cardiol* 2009;103:232–7.
- [10] Cappato R, Calkins H, Chen SA, et al. Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circulation* 2005;111:1100–5.
- [11] Practice guidelines for sedation and analgesia by non-anesthesiologists. A report by the American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. *Anesthesiology* 1996;84:459–71.
- [12] Gasparovic S, Rustemovic N, Opacic M, et al. Clinical analysis of propofol deep sedation for 1104 patients undergoing gastrointestinal endoscopic procedures: a three-year prospective study. *World J Gastroenterol* 2006;12:327–30.
- [13] Kennedy RM, Porter FL, Miller JP, et al. Comparison of fentanyl/midazolam with ketamine/midazolam for pediatric orthopedic emergencies. *Pediatrics* 1998;102:956–63.
- [14] Pena BM, Krauss B. Adverse events of procedural sedation and analgesia in a pediatric emergency department. *Ann Emerg Med* 1999;34:483–91.
- [15] Timmermans C, Ayers GM, Crijns HJ, et al. Randomized study comparing radiofrequency ablation with cryoablation for the treatment of atrial flutter with emphasis on pain perception. *Circulation* 2003;107:1250–2.
- [16] Tang RB, Dong JZ, Zhao WD, et al. Unconscious sedation/analgesia with propofol versus conscious sedation with fentanyl/midazolam for catheter ablation of atrial fibrillation: a prospective, randomized study. *Chin Med J (Engl)* 2007;120:2036–8.
- [17] Herr KA, Garand L. Assessment and measurement of pain in older adults. *Clin Geriatr Med* 2001;17:457–78 [vi].